days. Six weeks later, without any warning, the œdema returned. I promptly bled her from the elbow, with the most happy result. Her confinement is expected at any day.[55]

CONCLUSIONS. 1. There is an acute pulmonary œdema that comes on without any apparent exciting cause and often kills in a short time.

2. Recovery from an attack is frequent; but there is a striking tendency to recurrence, subsequent attacks being similar to the first. They set in suddenly, usually at night, and place the patient's life in jeopardy.

3. The clinical causes are various: arteriosclerosis and cardiac and renal disease are most important.

4. The pathogenesis is obscure; vasomotor disturbances and a disproportionate activity of the two ventricles (the right predominating) are the chief factors.

5. The chief symptoms are agonizing dyspnœa, cyanosis, cough, expectoration of frothy albuminous fluid, and profound prostration. Over the lungs, often more over the upper than the lower portions, the characteristic moist rales of edema are heard.

6. The most valuable remedies are bleeding, dry cupping, and cardiac stimulants.

7. The condition is of sufficient importance to warrant its having a special chapter in the text-books of medicine.

THE NATURE OF APLASTIC ANEMIA AND ITS RELATION TO OTHER ANEMIAS.[1]

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(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

APLASTIC anemia was first described by Ehrlich[2] in 1888. Since that time isolated cases have been reported and recently the condition has received considerable attention. The following typical case occurred in the University Hospital in the service of Dr. Stengel, to whom I am indebted for the clinical data.

J. C., female, aged thirty-three years, white, married, was admitted to the University Hospital December 18, 1905, complaining chiefly of palpitation of the heart and vomiting after taking food.

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[55] Since writing this she was delivered without any difficulty by Dr. V. A. Loeb, to whom I transferred her for this purpose; she has had no other attacks.

[1] Read at the meeting of the Association of American Physicians, Washington, D. C., May 15 and 16, 1906.

[2] Charité Annalen, 1888, xiii.

Previous Medical History. The patient had measles, whooping-cough, and chicken-pox during childhood; diphtheria at twenty-two years; "congestion of the lungs" at twenty-five years. Menstruation began at eleven years, and has always been regular and at times painful. For the past eleven years, since her last child was born, the discharge has lasted about a week and has been profuse. The patient says that until the onset of the present illness she has always been robust.

Social History. The patient was married at the age of nineteen years, and is the mother of two healthy children, respectively twelve and eleven years of age. She had one miscarriage three years ago, apparently induced by severe exertion. Her work has been confined to household duties.

Family History. The patient's father died of "liver abscess" at the age of thirty-eight years. Her mother is living and well at fifty-seven years. Four sisters are living and well. There is in the family no history of tuberculosis, cardiac or renal disease, or neoplasm, and no condition similar to that of the patient.

History of Present Illness. The present trouble dates from about eight weeks ago, when the patient noticed that she was becoming pale, objects appeared yellow to her, and she was constantly fatigued. Six weeks ago she began vomiting after taking food. This vomiting was inhibited by her lying down. Shortly after the vomiting commenced cardiac palpitation and dyspnœa on the slightest exertion made their appearance, and the patient noticed that she was becoming progressively paler and weaker. She judges that in the past eight weeks she has lost about twenty pounds. During the last week she has had six attacks of temporary unconsciousness lasting about five minutes each. They were induced by no apparent cause. She has not fallen in the attacks, has not bitten her tongue, and has had no convulsive movements during the attack. Her appetite is poor and the bowels constipated. She has sour eructations and vomits on the slightest exertion or excitement. She has noted no discharge of blood from the mucous membranes. The feet have not been swollen.

Physical Examination. The patient is a large-framed woman with subcutaneous fat well preserved. The contrast between the degree of nutrition and the degree of anemia is very striking. The skin is of a lemon-yellow color, the mucous membranes are universally pale.

There are no areas of hemorrhage in the skin or visible mucous membranes. There is no enlargement of the thyroid, or of the cervical, axillary, or epitrochlear glands. No jaundice. Pupils are equal and react sluggishly to light. The patient complains of some loss of vision in the left eye. Teeth are imperfect and carious. Thorax is well-formed. Pulmonary resonance extends anteriorly from one inch above the clavicle to the lower border of the sixth rib in the midclavicular line on the right; to the middle of the fourth rib on the left; posteriorly on the right, to the tenth dorsal vertebra; on the left, to the angle of the scapula. Below the angle of the scapula the resonance is somewhat impaired down to the tenth dorsal vertebra. In this area fremitus is diminished and breath sounds are feeble. No rales are heard. This area of diminished breath sounds extends anteriorly to the midaxillary line. In the remaining pulmonary area the breath sounds and fremitus are normal. The usual band of resonance over the shoulder is present on both sides. The physiological difference in breath sounds between right and left apex is less marked than usual.

The right border of the heart dulness is at the right border of the sternum; upper border, middle of fourth rib; left border, one inch outside of the left midclavicular line in the fifth interspace. The apex-beat is in the fifth interspace three-fourths of an inch inside of the midclavicular line. No thrills are present. There is a soft systolic murmur at the apex, heard also at the base, and most intense at the fourth interspace one inch to the right of the sternum. There is a slight accentuation of the pulmonic second sound. There is a continuous murmur heard over the innominate artery resembling a venous hum in its rhythm. There is also a dull venous hum high in the neck, over the jugular vein.

The abdominal walls are thick, but the abdomen is neither distended nor retracted. The liver dulness extends from the lower border of the sixth rib to within one inch of the costal margin in the midclavicular line. It is not palpable. Neither kidney is palpable. No tumor is discovered in the abdomen. The spleen is not enlarged, extends from the eighth to the tenth rib. It is not palpable. Nervous examination reveals no irregularities of reaction or sensation.

Urine Analysis. Amber, clear, slightly acid; specific gravity, 1010; slight trace of albumin; no sugar.

Gastric Analysis. Free HCl, 36. Total acidity, 64. No lactic acid. No Oppler-Boas bacilli.

Feces Analysis. Stool is yellow, hard, and alkaline. Contains considerable vegetable detritus, a small amount of casein, triple phosphates, and a small amount of soap. Bile is present. There is no occult blood and no indication of the presence of parasites.

Blood Examination. Hemoglobin, 10 per cent.; red blood corpuscles, 800,000; white blood corpuscles, 2560; color index, 0.62. Differential count: lymphocytes, 67 per cent.; polymorphonuclear neutrophiles, 27 per cent.; polymorphonuclear eosinophiles, 0.4 per cent.; large mononuclear leukocytes, 3.5 per cent. No myelocytes were found. In counting over 1000 leukocytes, one normoblast was found. Despite repeated searches no megaloblasts were found. There were no microcytes. Very slight poikolocytosis, and no anisocytosis were found. Subsequent examination of the blood revealed but trivial variations from this count.

Ophthalmoscopic examination revealed a well-marked, low-grade neuroretinitis, with numerous hemorrhages of various size and shape lying in the nerve-fiber layer, and a few more deeply placed hemorrhages. The swelling of the left nerve head and obscuration of its edges was more marked than in the right eye.

Without the appearance of any new noteworthy symptoms, the patient grew progressively weaker and died with symptoms of œdema of the lungs eight days after admission, or approximately nine weeks after the onset. Permission for the autopsy, performed four days after death, was obtained through the efforts of Dr. F. H. MacFarland, to whom I am deeply indebted.

Autopsy. The macroscopic findings briefly stated were as follows: The body of a well-formed, well-nourished, adult female. Height approximately five feet three inches. Weight about one-hundred and thirty-five pounds. Subcutaneous fat moderately abundant, light yellow in color. Muscles of fair consistency and pale. The left pleural cavity contained 400 c.c. of serosanguineous fluid; the right pleural cavity approximately 200 c.c. of fluid of the same character. There was œdema of the lungs and fatty degeneration of the heart muscle. There were no valvular defects. In the pelvic peritoneal cavity were 200 to 300 c.c. of dark-red, fluid blood containing one small clot. The liver was anemic and fatty; the spleen pale, firm, and not enlarged; the kidneys pale and fatty. Aside from pallor of the mucous membranes the gastrointestinal tract presented no abnormalities. There were no evidences of the presence of parasites. In the mesentery and retroperitoneal tissues a few hemolymph nodes were found, light reddish-brown in color, and of the size of small beans. The marrow of the ribs was light yellow in color; that of both the diaphysis and epiphysis of the tibia, fatty and extremely pale.

Histological Examination. There was fatty degeneration of the heart muscle in the form of extremely fine globules of fat, and a considerable hemosiderin deposit, mostly in the protoplasm of the cells at both poles of the nucleus. The section of liver showed a marked fatty change in the form of large globules confined almost exclusively to the central half of the individual lobules. There was an extensive deposit of hemosiderin occurring diffusely throughout the liver cells. In the section of spleen, there was noted a moderate proliferation of endothelium within the pulp. The follicles were prominent but apparently not hypertrophied. A few normoblasts were visible in the section. In the kidney the epithelium of the tubules of the cortex showed some disintegration and in many areas was detached from the basement membrane. Numerous small fat globules were present in the epithelium of the tubules, especially toward the free margins of the cells. The lumina were filled with a granular exudate including, here and there, shadows of red blood corpuscles. The hemolymph glands showed the peripheral sinuses to be small and there was some endothelial proliferation in the pulp. Smears and sections were made of the bone-marrow of the shaft of the tibia near the epiphysis. They both showed a large amount of fat, a very few normoblasts and normocytes, an absence of megaloblasts, a moderate number of lymphocytes, and a few myelocytes. No polymorphonuclear leukocytes could be identified.

I have succeeded in collecting from the literature ten cases in which the clinical phenomena and postmortem findings warrant their being considered cases of aplastic anemia. They are as follows:

Case I.—Bloch.[3] Female, aged sixty-three years; first symptoms noted, weakness and pallor; duration, six weeks. Blood: hemoglobin, 28 per cent.; red blood corpuscles, 1,970,000; leukocytes, 3250. Differential count: lymphocytes greatly preponderating; no nucleated red blood corpuscles; a few microcytes; no megalocytes; color index, 0.71. Postmortem findings: marrow of long bones showed no lymphoid hyperplasia; in marrow of ribs there were no megaloblasts. Prominent clinical feature: four days before death hemorrhage from buccal mucous membrane.

Case II.—Bloch.[4] Female, aged fifty-three years; first symptom noted was weakness. Blood: severe anemia, marked reduction in leukocytes, those persisting being almost entirely lymphocytes. No megaloblasts; after prolonged search a few normoblasts were found. Postmortem findings: marrow of shafts of long bones pale and fatty. Marrow of epiphyses of normal red color. Prominent clinical feature: numerous gastric hemorrhages occurred during the course of the disease.

Case III.—Ehrlich.[5] Female, aged twenty-one years; metrorrhagia eighteen days before onset. Blood: hemoglobin, very low; red blood corpuscles, 213,360; white blood corpuscles, greatly reduced. Differential count: lymphocytes, 80 per cent.; polymorphonuclear neutrophiles, 14 per cent.; large mononuclear leukocytes, 3 per cent.; eosinophiles, 0; no nucleated red blood corpuscles. Postmortem findings: bone-marrow yellow in shafts of long bones, slightly pinkish in diaphyses. No megaloblasts. No normocytes. Very few normoblasts and myelocytes. No polynucleated granulated cells.

Case IV.—Engel.[6] Female, aged thirty-one years; shortly before onset blood noted in stools and hemorrhage from gums; duration, three weeks. Blood: hemoglobin, 18 per cent.; red blood corpuscles, 2,115,000; white blood corpuscles, greatly reduced. Differential count: small lymphocytes, 90 per cent.; polymorphonuclear neutrophiles, 7 per cent.; no microcytes; no macrocytes; no nucleated red blood corpuscles. Color index, 0.42. Postmortem findings: diaphyses and epiphyses of long bones yellow and fatty. Microscopically, nothing but fat. Marrow of ribs gray and watery. No cells present. Prominent clinical feature: there was a doubtful history of swallowing of corrosive shortly before the onset of symptoms. Chief complaint was weakness.

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[3] Ziegler's Beiträge, 1903, xxiv, 331.

[4] Ibid.

[5] Loc. cit.

[6] Ztschr. f. klin. Med., 1900, ii.

Case V.—Evans and Halton.[7] Male, aged thirty-six years; first symptoms noted shortly after bleeding from nose lasting two and one-half hours; duration, two months. Blood: hemoglobin, 10 per cent.; red blood corpuscles, 770,000; white blood corpuscles, 2300. Differential count: polymorphonuclear neutrophiles, 6 per cent.; small lymphocytes, 90 per cent.; large lymphocytes, 4 per cent.; eosinophiles, none; no nucleated red blood corpuscles. No marked poikilocytosis. Shortly before death two nucleated red blood corpuscles were found; color index, 0.65; actual number of lymphocytes, 2070. Postmortem findings: skull bones showed fatty marrow with very few cells. Prominent clinical features: chief complaint was weakness and faintness.

Case VI.—Hirschfeld.[8] Female, aged twenty-eight years; onset shortly after delivery; duration, nine months. Blood: red blood corpuscles, 1,200,000; white blood corpuscles, 3600. Differential count: small lymphocytes, 72 per cent.; no eosinophiles; no nucleated red blood corpuscles; actual number of lymphocytes, 2592. Postmortem findings: bone-marrow universally yellow; bone-marrow was composed chiefly of small lymphocytes, a very few granulated cells, and a few normoblasts. Prominent clinical features: numerous small hemorrhages into the skin, mucous membranes, and retina occurred during the course; menstruation was extremely profuse.

Case VII.—Muir.[9] Male, aged fourteen years; the first symptoms noted were vomiting of blood, bleeding from nose, and hemorrhages into skin; duration, eleven weeks. Blood: hemoglobin, 12 per cent.; red blood corpuscles, 800,000; white blood corpuscles, 7000. Differential count: lymphocytes, 70 per cent.; polymorphonuclear neutrophiles, 25 per cent.; no nucleated red blood corpuscles; color index, 0.75; actual number of lymphocytes, 4900. Postmortem findings: bone-marrow fatty; very few nucleated red blood corpuscles or other normal cells of bone-marrow.

Case VIII.—Pasteur.[10] Male, aged twenty-four years; first symptom was pain in epigastrium; duration, seven weeks. Blood: hemoglobin, 20 per cent.; red blood corpuscles, 1,090,000; white blood corpuscles, 2600. Differential count: lymphocytes, 74 per cent.; polymorphonuclear neutrophiles, 20 per cent.; hyaline and transitional cells, 6 per cent.; no megaloblasts; color index, 0.91; actual number of lymphocytes, 1924. Postmortem findings: bone-marrow, pale; no polymorphonuclear leukocytes.

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[7] Jour. Amer. Med. Assoc. 1905, i, 1195.

[8] Deut. med. Woch., 1904, xxii, 650.

[9] Brit. Med. Jour. September 29, 1900.

[10] Lancet, November 21, 1903.

CASE IX.—Zeri.[11] Female, aged fifty-seven years; first symptoms noted were hemorrhages into skin; duration, six months. Blood: hemoglobin, 20 per cent.; red blood corpuscles, 1,300,000; white blood corpuscles, 3580. Differential count: polymorphonuclear leukocytes were scarce in comparison to lymphocytes; no macrocytes; no megaloblasts; two normoblasts were found; color index, 0.76. Postmortem findings: marrow of long bones yellow in both diaphysis and epiphysis; the same in costal and vertebral bones. Prominent clinical features: during the course of the disease patient had prolonged epistaxis and numerous hemorrhages into skin.

CASE X.—Zeri.[12] Male, aged forty-six years; onset preceded by diarrhœa; duration, three months. Blood: hemoglobin, 38 per cent.; red blood corpuscles, 1,423,000; white blood corpuscles, 2700. Differential count: polymorphonuclear leukocytes and transitional cells, 57 per cent.; eosinophiles, 0; later moderate poikilocytosis; a few microcytes and macrocytes; no nucleated red blood corpuscles; color index, 1.33; actual number of lymphocytes, 1161. Postmortem findings: marrow of flat bones, orange yellow; of long bones, in both epiphysis and diaphysis, yellow and fatty; scarcity of polymorphonuclear leukocytes; normoblasts with multiform nuclei were present; in the marrow of the shafts of the long bones degeneration and proliferation of connective tissue.

Making a composite case from these ten cases and my own, we obtain one of the following characteristics: age, thirty-seven years; duration, three months. Blood: hemoglobin, 18 per cent.; erythrocytes, 1,116,600; leukocytes, 3574; lymphocytes, 73 per cent.; actual number of lymphocytes, 2393; color index, 0.77. It is readily seen that the more prominent features of such a case are sufficiently marked to furnish a very striking clinical picture, associated with unique postmortem findings.

The disease, as characterized by the cases quoted shows itself to be first manifested by symptoms common to any profound anemia: ready exhaustion, dyspnœa, disturbance of vision, tinnitus, nausea, and vomiting. In a strikingly large percentage of cases, considerable or numerous small hemorrhages occur shortly before, or coincident with, the onset of the symptoms of anemia, as noted by the patient. The patient usually remains fairly well nourished as far as the bulk of the fixed tissues, particularly the fat, is concerned, and there is a striking disharmony between the quality of the patient's blood and state of bodily nourishment. Usually without any prominent symptoms referable to any other system or function, the patient grows progressively weaker, and in from two to four months dies. Naturally the most noteworthy picture is afforded by the blood analysis, in which there is a profound reduction in the amount of hemoglobin and a somewhat less marked reduction in the number of red blood corpuscles, an absence or a remarkably small number of normoblasts, a total absence of megaloblasts, and a leukopenia associated with a relative lymphocytosis.

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[11] Il Policlinico, s. m. fasc. vii, 1905.

[12] Ibid.

At autopsy, aside from the findings purely incidental to the grade of the anemia, there is the characteristic feature in the bone-marrow, which is intensely pale and fatty and lacks the evidences of blood regeneration.

A critical review of these more prominent symptoms immediately suggests the question that has been the source of some argument in regard to aplastic anemia, namely, its relation to progressive pernicious anemia. The onset of the disease, its course, excepting as to the rapidity of a lethal termination, the absence of any marked loss of substance in the fixed tissues, and the great reduction in the amount of hemoglobin and the number of red corpuscles, are common to both conditions. In our attempt to determine the relation between aplastic anemia and progressive pernicious anemia, let us discuss individually the phenomena at variance in the two conditions. Probably the most striking of these, and surely the most important, is the blood picture in which we find an almost complete absence in aplastic anemia of nucleated red blood corpuscles and the total absence of megaloblasts. Since the red corpuscles are a product of the bone-marrow, a consideration of them will necessarily involve a consideration of the bone-marrow. There is by no means a unity of opinion as to the primary effect of the etiological agent in pernicious anemia in its relation to the bone-marrow. Rindfleisch and Cohnheim[13] look upon the bone-marrow changes as primary, while others (Neumann, Litten, Orth) consider them as secondary, in the nature of an attempt on the part of the bone-marrow to compensate for the destruction of red blood corpuscles. Just as the character and number of the atypical red blood corpuscles vary in different cases of anemia, so does the character of the bone-marrow differ (see accompanying plate). In one case there is a red jelly-like marrow (megaloblastic degeneration) composed almost entirely of megaloblasts and associated with the presence of numerous megaloblasts in the circulating blood; in another case, but few megaloblasts and correspondingly little red marrow in the shafts of the long bones. In a case that I recently autopsied, there were a very moderate number of normoblasts and megaloblasts, and at the autopsy the shafts of the long bones were found to be fatty with islands of red scattered here and there through it. It is thus seen that deductions as to the condition of the bone-marrow can frequently be drawn from a consideration of the cells of the circulating blood.

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[13] Virchow's Archiv, lxvii, 291.

What of these relations in aplastic anemia? I have said that the blood shows an extremely limited number of nucleated red blood corpuscles, and we would consequently expect to find, as we in fact do, a pale bone-marrow in which the evidences of new blood formation are entirely wanting. We see, then, that in aplastic anemia there is a blood picture which is but a reflection of the condition of the bone-marrow, in which evidences of regeneration are entirely lacking, but in which there is no indication that the determining factor in the causation of the disease acts in any way different from that of the usual type of progressive pernicious anemia. It is but a difference in response of the organism to the causative agent.

What of the color index which in typical progressive pernicious anemia is considered to be characteristically high, and in aplastic anemia has been in all cases, excepting one, considerably below 1, and averages in all the cases 0.77? In progressive pernicious anemia, aside from megaloblasts, there are non-nucleated red blood corpuscles of considerably more than normal size, megalocytes. Laache has offered the usually accepted explanation for the high color index in progressive pernicious anemia in the large number of these abnormal cells present, which containing more hemoglobin than the normal cell naturally raise the color value. As has been remarked, in aplastic anemia there is usually little anisocytosis, and with the absence of both megaloblasts and megalocytes, it is readily seen why, on the basis of Laache's theory, the color index should not be raised above the normal. An interesting theory for the high color index in progressive pernicious anemia is proposed by Schaumann.[14] He considers that some of the iron deposited as hemosiderin in the liver and spleen is taken up by the existing corpuscles, used as a nucleus for the formation of more hemoglobin, and thus each individual corpuscle bears more than the normal amount. Some weight is lent to this view by experiments of Tallqvist.[15] In experimental anemias in dogs he showed that the color index was higher in cases of slow growing anemia than in those of rapid growth, and in the former the siderosis was greater than in the latter. This theory would also explain the low color index in cases of aplastic anemia, as they have almost all been of extremely rapid course.

Let us consider for a moment this more rapid course and invariably fatal termination of aplastic anemia with the course and termination in progressive pernicious anemia. We have seen that in aplasic anemia destructive forces are at work as in progressive pernicious anemia, but the regenerative process present in the latter is wanting in the former. If a destructive process be active and there be no constructive process to counteract it, it is but a natural consequence that, other things being equal, exhaustion will more readily result than if there be constructive changes.

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[14] Berl. klin. Woch. 1899, Nos. 1 and 3.

[15] Ueber experimentelle Blutgiftanæmien, Berlin, 1900.

Another feature at variance in the two conditions is the number of leukocytes and the proportions to one another of the various forms of leukocytes. In uncomplicated cases of progressive pernicious anemia the leukocytes average from 5000 to 6000; in aplastic anemia they average 3574. What is even more striking than this difference is the difference in the percentage of lymphocytes. In progressive pernicious anemia the lymphocytes vary from 37 per cent. (Strauss and Rohnstein[16]) to 31 per cent. (McCrae), while in aplastic anemia they average 73 per cent. A discussion of the principles underlying this variance must be prefaced by a few words concerning the origin of leukocytes. It is generally conceded that the granulated leukocytes, *i. e.*, the polymorphonuclear leukocytes and their progenitors, the myelocytes, have their origin in the bone-marrow; but there has been a vigorous discussion existing for some time as to whether the lymphocytes be the product of the bone-marrow or of the other more distinctly lymphatic structures, lymph glands, spleen, and lymphatic tissue of the gastrointestinal tract. Ehrlich believes firmly in the origin of the lymphocytes from true lymphatic structures, while others claim them to be of common origin with the granulated cells. That lymphocytes are formed in the bone-marrow there can be little doubt, for wherever lymphoid tissue is present, lymphocytes are produced; and, as was shown by Arnold and Ribbert, there is an element of lymphatic tissue in almost every organ of the body. So although lymphocytes may be produced in the bone-marrow by reason of the participation of the bone-marrow in the general distribution of lymphatic tissue, I do not believe that the production of lymphocytes is a specific function of it. Let us observe what bearing the lymphocytes in aplastic anemia have upon the question. We have seen that the red blood corpuscles and the granulated leukocytes, both admittedly products of the bone-marrow, are enormously reduced. But what of the lymphocytes? We have seen that in the average case of aplastic anemia there are 2393 lymphocytes, and it will be observed that this differs but slightly from the average normal number of lymphocytes, about 2200. Does it not seem irrational that if the lymphocytes be an integral part of the bone-marrow they should be so slightly affected and the other bone-marrow elements so profoundly reduced? As to the relation between the percentage of lymphocytes in progressive pernicious anemia as compared with that of aplastic anemia, I look upon it that in neither condition are they actually materially affected. In progressive pernicious anemia they are, on the average, approximately 35 per cent. of the total number of leukocytes, 5000 to 6000, which is but little less than 73 per cent. of 3574, the total average number of leukocytes in aplastic anemia. The difference depends entirely upon the variations in the number of polymorphonuclear neutrophiles and in harmony with the generally more intense character of the lesions in aplastic anemia they are more markedly reduced than in the former.

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[16] *Die Blutzusammensetzung bei den verschiedenen Anämien.*

In regard to the autopsy findings the essential differences in the two diseases lie in the bone-marrow, which, as we have attempted to show in the above analysis, manifests a complete failure of regeneration on its part.

Basing our deductions upon the above comparison, we thus see that progressive pernicious anemia is associated with regenerative processes which in aplastic anemia are lacking. As to the destructive processes, it has been shown by Hunter, Quincke, Pepper and Stengel that progressive pernicious anemia is primarily a hemolytic disease. That aplastic anemia is of the same nature, may be accepted by reason of the consistent occurrence of hemorrhages in practically all of the cases reported, and by reason of the hemosiderosis present in our case. It is unfortunate that in the previously reported cases no mention is made of this condition. We see, then, that the blood picture in aplastic anemia and the course of the disease are the result of two factors: the one the hemolysis, the other the failure of regenerative changes to compensate for this destruction. The failure of regeneration by the bone-marrow may be dependent upon one of the following three factors: first, a simple deficiency of the regenerative powers; second, an inhibitive action on the bone-marrow by the factors producing the destruction of the blood elements; third, a true aplasia of the bone-marrow. If the latter be the case, the aplasia is probably of recent origin, for if it were of long duration there would, in all probability, have been manifestations of a deficiency in blood formation before the advent of the hemolytic agent.

It will be necessary to discuss but briefly the relation that aplastic anemia bears to simple anemia. Lazarus looks upon aplastic anemia as a variety of simple anemia, basing his view upon the fact that aplastic anemia is most like simple anemia in the blood picture. A review of the cases that we have collected reveals the fact that in practically none of the cases has there been the history of the various organic diseases so frequently associated in an etiological way with simple anemia. It is true that hemorrhages do appear to have been more frequent and probably more profound in aplastic anemia than in progressive pernicious anemia, but that they stand in an etiological relation to aplastic anemia can scarcely be entertained. They have occurred throughout the course of the disease rather than precedent to it, and as Birch-Hirschfeld[17] has emphasized, the severity of the anemia stands in marked contrast to the amount of hemorrhage, though it must be admitted that in some cases when hemorrhages are small and numerous, and especially when they occur in the gastrointestinal tract, a calculation of the amount of blood lost is difficult or impossible; but the most important elements differentiating aplastic anemia from simple anemia are furnished by a consideration of the clinical features of aplastic anemia. It is an essentially pernicious disease in course, duration, and termination, and serves well to illustrate the futility of attempting the diagnosis of most blood diseases on the blood picture alone.

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[17] Verhandl. d. Congress f. innere Medizin, Wiesbaden, 1892, xi.

The exclusion from our list of a number of cases that have been reported as cases of aplastic anemia, or present otherwise features suggestive of this disease, requires some words of justification.

Senator[18] reports the case of a girl, aged thirteen years, complaining, chiefly of weakness and vertigo. The disease was of three months' duration, and the blood findings were as follows: hemoglobin, 8 to 10 per cent.; erythrocytes, 1,040,000; leukocytes, 8000; poikilocytosis; no nucleated red blood corpuscles; no eosinophiles. The majority of the white blood corpuscles were lymphocytes. Blood from the heart, taken at autopsy, showed 728,000 red blood corpuscles and 11,200 white blood corpuscles, of which 83.6 per cent. were lymphocytes. At autopsy the bone-marrow was found to be universally red, showing microscopically large numbers of lymphocytes and a few normoblasts. Two elements in this case tend to exclude it from the aplastic anemias. The one is the metaplastic bone-marrow, containing numerous lymphocytes, the other the occurrence clinically of a considerable actual increase of the lymphocytes, as is shown by the fact that 83.6 per cent. of 11,200 leukocytes were lymphocytes. Senator himself says of the case, after a consideration of the clinical and postmortem features, "we are thus dealing with a case of myelogenous pseudoleukemia, and according to the present-day terminology one of a pure medullary form, since the lymphatic glands were not at all, and the spleen to a very moderate degree, swollen."

Blumer[19] reports a case of twenty-two months' duration, occurring after the loss of considerable blood from hemorrhoids. The blood showed 20 per cent. of hemoglobin, 1,516,000 red blood corpuscles, and 4000 white blood corpuscles, of which 88.3 per cent. were lymphocytes. An average of one normoblast to a field was found. At autopsy the bone-marrow of the upper part of the tibia was yellow, that of the ends of the other long bones partly red and partly fatty. On the basis of a duration of twenty-two months, which is more than seven times the average duration, and the presence of a considerable number of normoblasts, in harmony with which is the partly red and partly yellow bone-marrow of the diaphyses, we feel justified in looking upon this as a doubtful case of aplastic anemia. It has more of the features, excepting for the percentage of lymphocytes, of a low grade normoblastic progressive pernicious anemia.

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[18] Ztschr. f. klin. Med., lix, 1.

[19] Bull. Johns Hopkins Hospital, April, 1905.

Schaumann's[20] case, which he reports as aplastic anemia, is very suggestive, but the data furnished in the report of the case are insufficient to warrant the diagnosis.

The case of Pane,[21] quoted by Zeri as a case of aplastic anemia, is doubtful. The meager clinical data furnished, associated with the finding postmortem of a splenic tumor, and hyperplasia of Peyer's patches and the solitary follicles of the intestinal tract, do not justify us in considering the case one of aplastic anemia.

Wolff's[22] case presents, as he himself says, "more features of an aplastic leukemia than an aplastic anemia."

Escherich[23] reports a case of anemia in a child, aged four years, that strongly suggests aplastic anemia. The disease was of six months' duration. The red blood corpuscles varied between 575,000 and 737,500; the hemoglobin between 10 and 15 per cent.; the leukocytes between 3500 and 7000. The statement is made that the majority of white blood corpuscles were lymphocytes. There was considerable poikilocytosis and macrocytosis and no nucleated red blood corpuscles. There was at first some swelling of the lymphatic glands in the region of the mastoid and in the left axilla. It is to be regretted that there was no postmortem examination to confirm the strong suggestion of its having been a case of aplastic anemia.

Kurpjeweit[24] has recently reported two cases of anemia in the aged, which present some features suggestive of aplastic anemia, especially the first case. However, the greatly enlarged spleen, measuring 18.5 cm. x 12.5 cm. x 6 cm., and the but moderately severe course of the disease, together with the lack of leukocytic examination in the case, will not permit of a diagnosis of aplastic anemia. The second case also had a remarkably large spleen, 800 grams. Lymphocytes did not preponderate, and the bone-marrow showed normoblastic regeneration.

CONCLUSIONS. 1. Aplastic anemia is a variety of progressive pernicious anemia.

2. The essential features of aplastic anemia are: a rapidly fatal course; a marked reduction in the number of red blood corpuscles; a greater proportionate reduction in the amount of hemoglobin, resulting in a low color index; a leukopenia with a relative lym-

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[20] Volkmann's Sammlung klinischer Vorträge, n. f. No. 287.

[21] Riforma Medica, 1900, xvi, No. 4.

[22] Berl. med. Woch., 1905, xlii, No. 2.

[23] Wien klin. Woch., 1892, Nos. 13 and 14.

[24] Deut. Archiv. f. klin. Med., lxxxii, Nos. 5 and 6.

phocytosis; an absence of megaloblasts, and usually normoblasts. Postmortem: the characteristic finding is a pale bone-marrow in which the signs of erythrocytic and granulated leukocytic formation are wanting.

3. The differences between aplastic anemia and the usual form of progressive pernicious anemia result entirely from the absence of regenerative processes in the former.
4. The blood picture in aplastic anemia is the result of two factors, one the hemocytolysis, and the other the failure of regeneration on the part of the bone-marrow.
5. The failure of regeneration of the blood elements of the bone-marrow represents the result of one of the three following conditions: (*a*) A simple deficiency of the regenerative powers; (*b*) an inhibitive action on the bone-marrow by the factors producing the destruction of the blood elements; and (*c*) a true aplasia of the bone-marrow. If there be a true aplasia it is probably of recent origin, for if it were of long duration there would in all probability have been manifestations of a deficiency in blood formation before the advent of the hemolytic agent.
6. The relations of lymphocytes to leukocytes and red blood corpuscles in aplastic anemia lend evidence to the view that lymphocytes are not a specific product of the bone-marrow.

STUDIES IN THE NATURAL AND ARTIFICIAL INHIBITION OF PEPTIC DIGESTION.

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No matter how important the secretion of hydrochloric acid may be for the purpose of preparing the food for the action of pepsin, and for stimulating the production of pepsin and the secretion of the pancreatic, and probably of the intestinal juices, there can be no question, we think, that the actual work in the stomach of preparing the proteids for assimilation depends upon the peptic activity. Therefore it is exceedingly important in all cases of gastric disease to determine whether the peptic activity is normal or not, and whether, if it is normal under favorable experimental conditions, there may not be present in the gastric contents inhibitory factors which prevent, or make imperfect, the peptonization of the food.

A number of methods have been suggested for estimating the